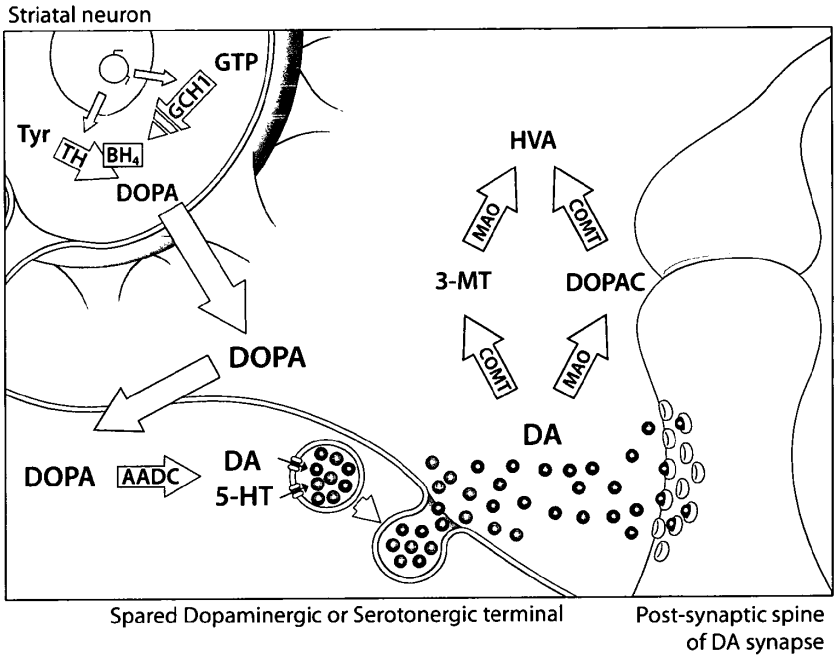
Continuous DOPA delivery strategy



Continuous DOPA delivery strategy

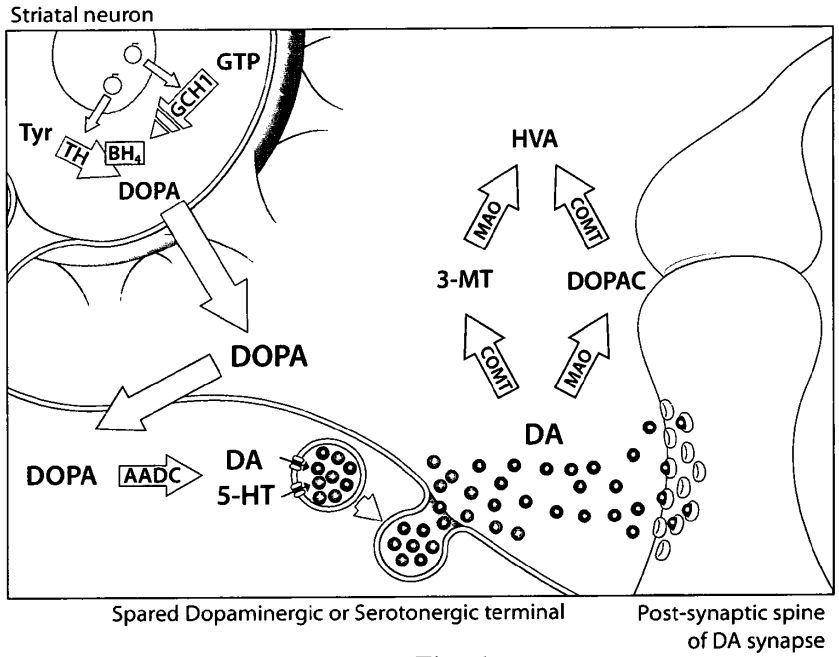


Fig. 1

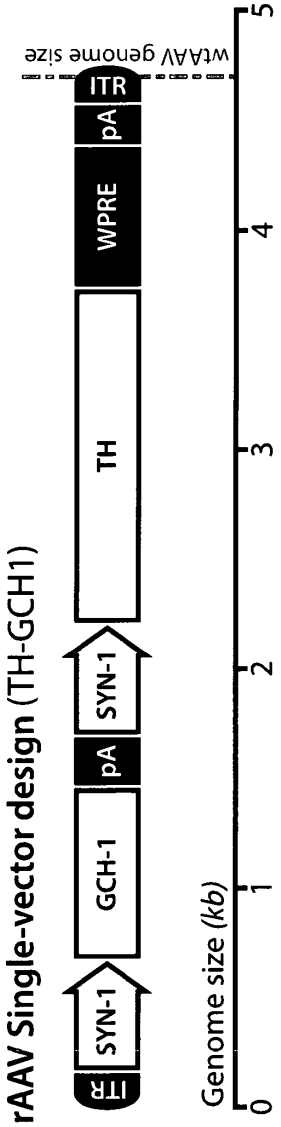

rAAV Single-vector design (TH-GCH1)
ITR
SYN-1
GCH-1
pA
SYN-1
TH
WPRE
pA
ITR
wtAAV genome size
Genome size (kb)
0
1
2
3
4
5

Fig. 2

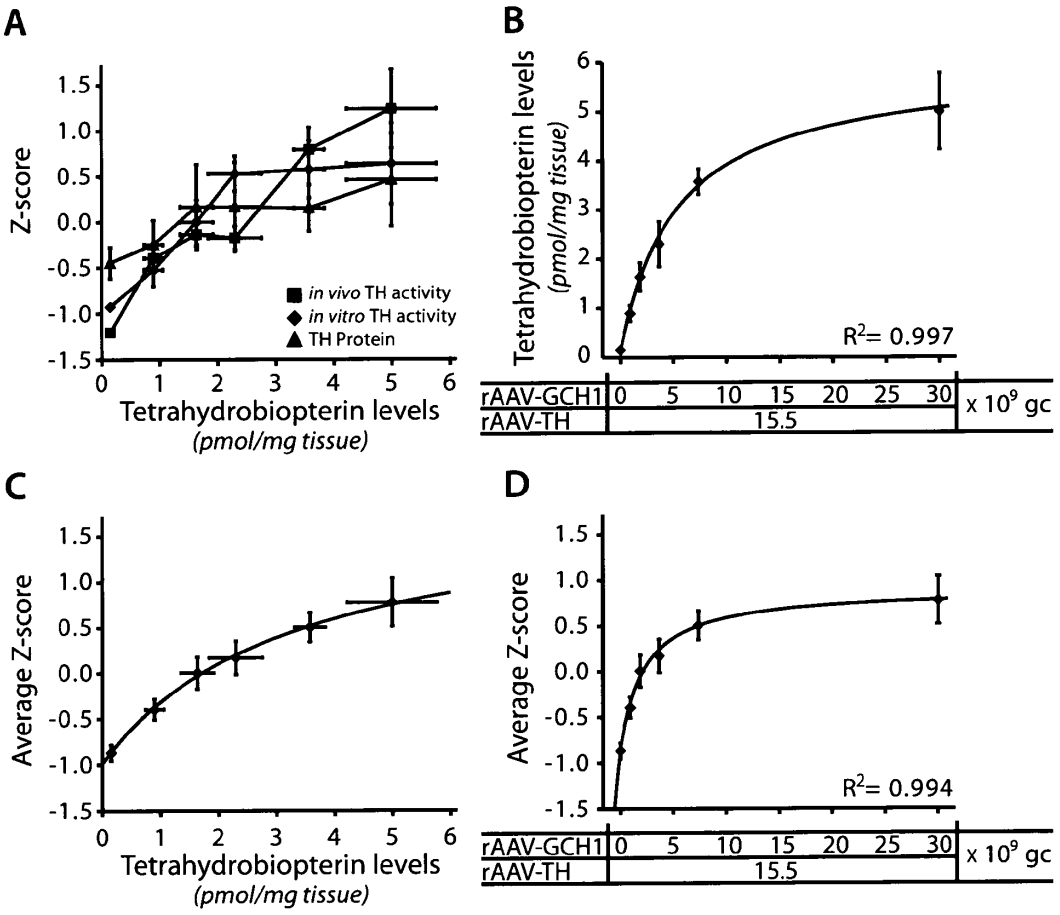

A
Z-score
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
0 1 2 3 4 5 6
Tetrahydrobiopterin levels
(pmol/mg tissue)
in vivo TH activity
in vitro TH activity
TH Protein
B
Tetrahydrobiopterin levels
(pmol/mg tissue)
6
5
4
3
2
1
0
R2= 0.997
rAAV-GCH1 0 5 10 15 20 25 30 x 10^9 gc
rAAV-TH 15.5
C
Average Z-score
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
0 1 2 3 4 5 6
Tetrahydrobiopterin levels
(pmol/mg tissue)
D
Average Z-score
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
R2= 0.994
rAAV-GCH1 0 5 10 15 20 25 30 x 10^9 gc
rAAV-TH 15.5

Fig. 3

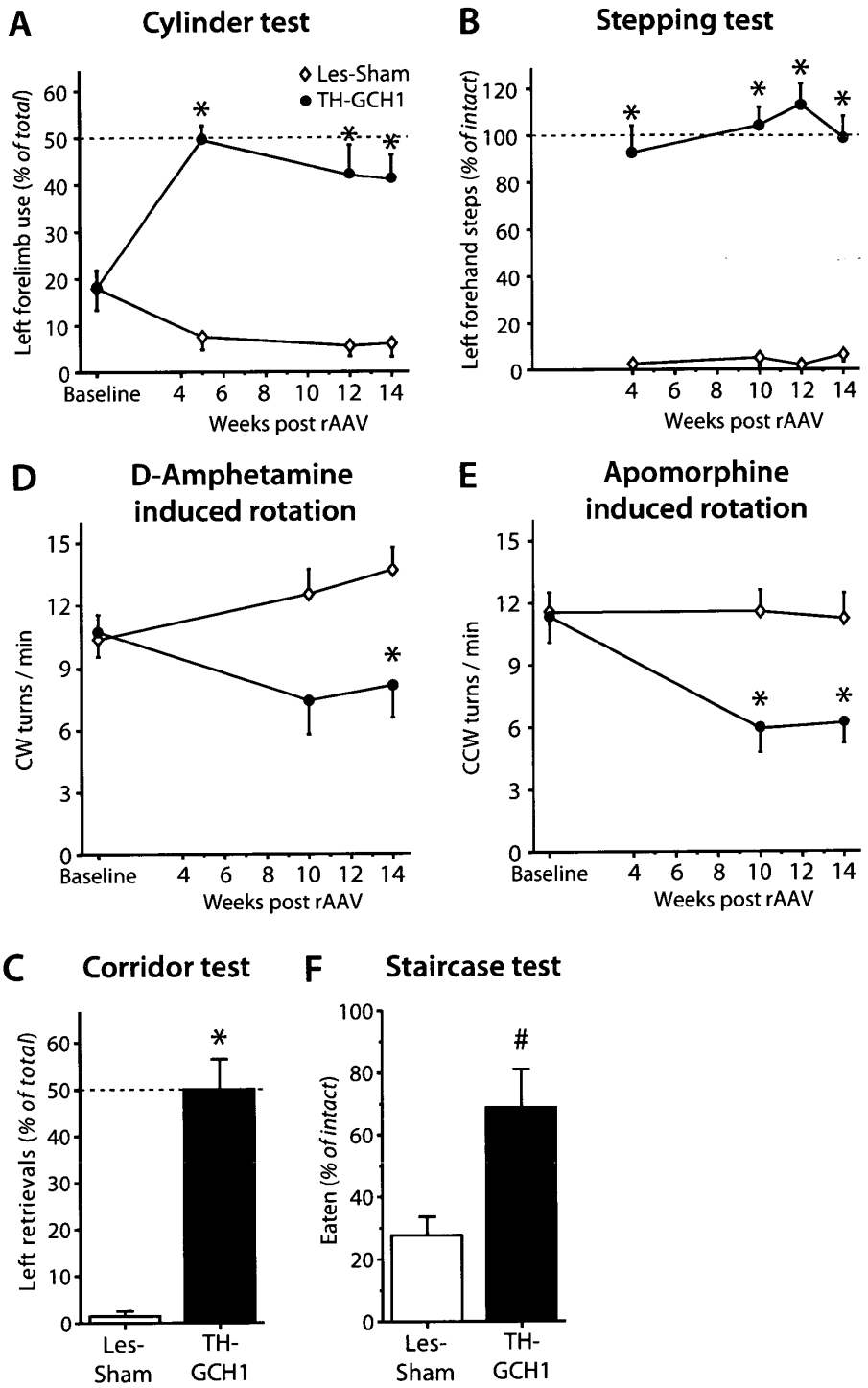

A
Cylinder test
◊ Les-Sham
● TH-GCH1
Left forelimb use (% of total)
Baseline
Weeks post rAAV
B
Stepping test
Left forehand steps (% of intact)
Weeks post rAAV
D
D-Amphetamine induced rotation
CW turns / min
Weeks post rAAV
E
Apomorphine induced rotation
CCW turns / min
Weeks post rAAV
C
Corridor test
Left retrievals (% of total)
Les-Sham
TH-GCH1
F
Staircase test
Eaten (% of intact)
Les-Sham
TH-GCH1

Fig. 4

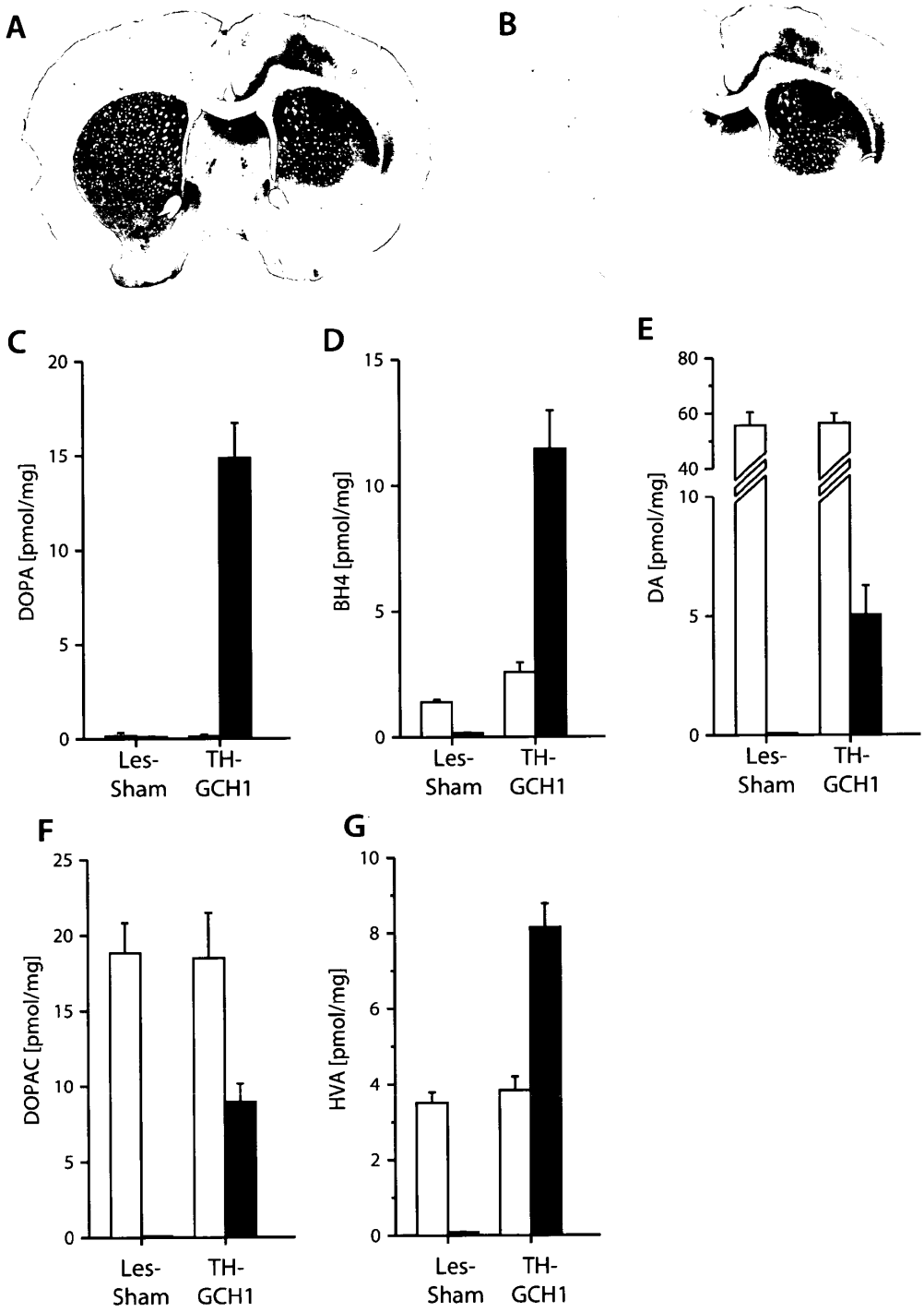

A
B
C
DOPA [pmol/mg]
20
15
10
5
0
Les-
Sham
TH-
GCH1
D
BH4 [pmol/mg]
15
10
5
0
Les-
Sham
TH-
GCH1
E
DA [pmol/mg]
80
60
40
10
5
0
Les-
Sham
TH-
GCH1
F
DOPAC [pmol/mg]
25
20
15
10
5
0
Les-
Sham
TH-
GCH1
G
HVA [pmol/mg]
10
8
6
4
2
0
Les-
Sham
TH-
GCH1

Fig. 5

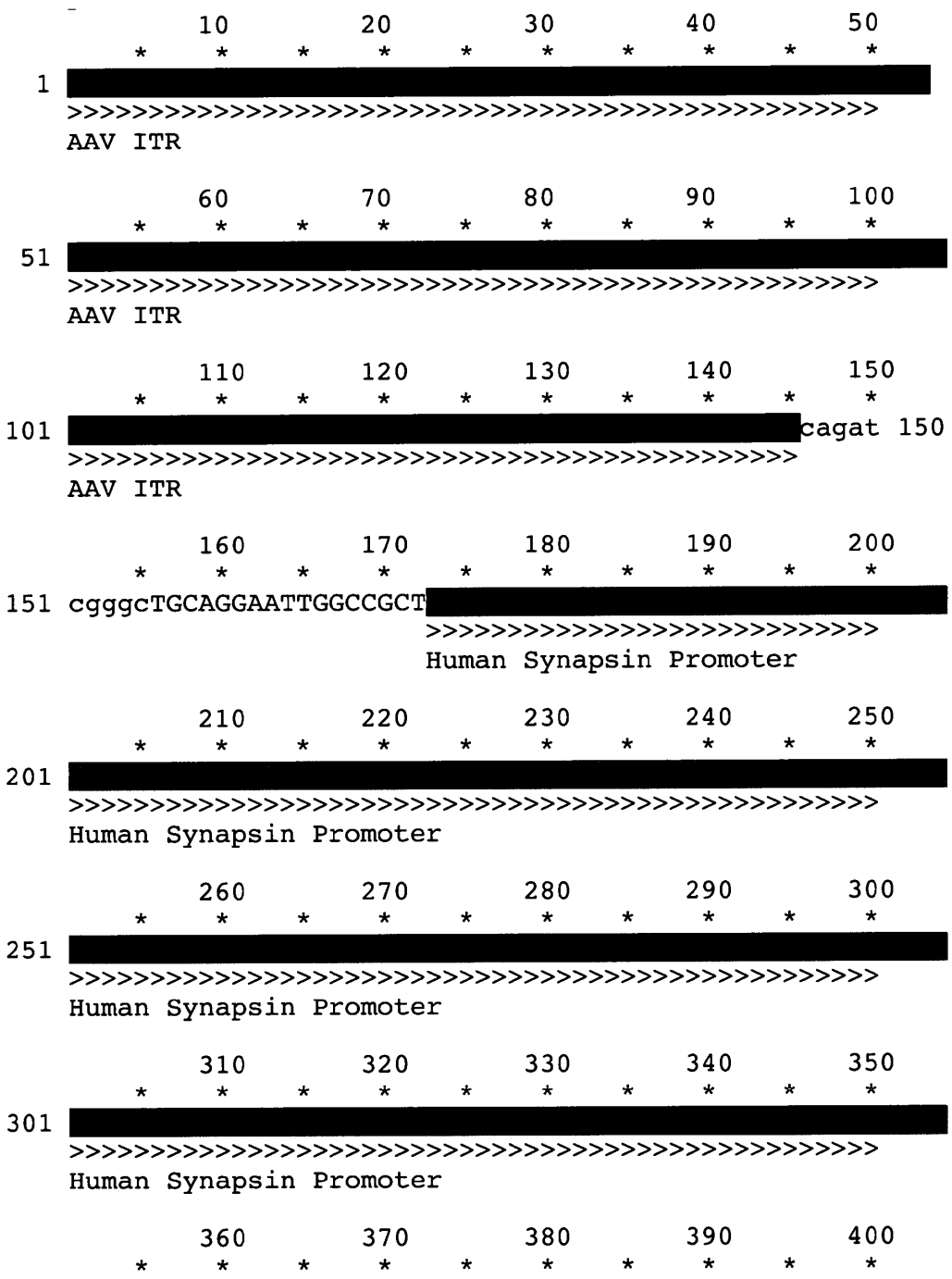

10 20 30 40 50
1
AAV ITR
60 70 80 90 100
51
AAV ITR
110 120 130 140 150
101
cagat 150
AAV ITR
160 170 180 190 200
151 cgggcTGCAGGAATTGGCCGCT
Human Synapsin Promoter
210 220 230 240 250
201
Human Synapsin Promoter
260 270 280 290 300
251
Human Synapsin Promoter
310 320 330 340 350
301
Human Synapsin Promoter
360 370 380 390 400

Fig. 6

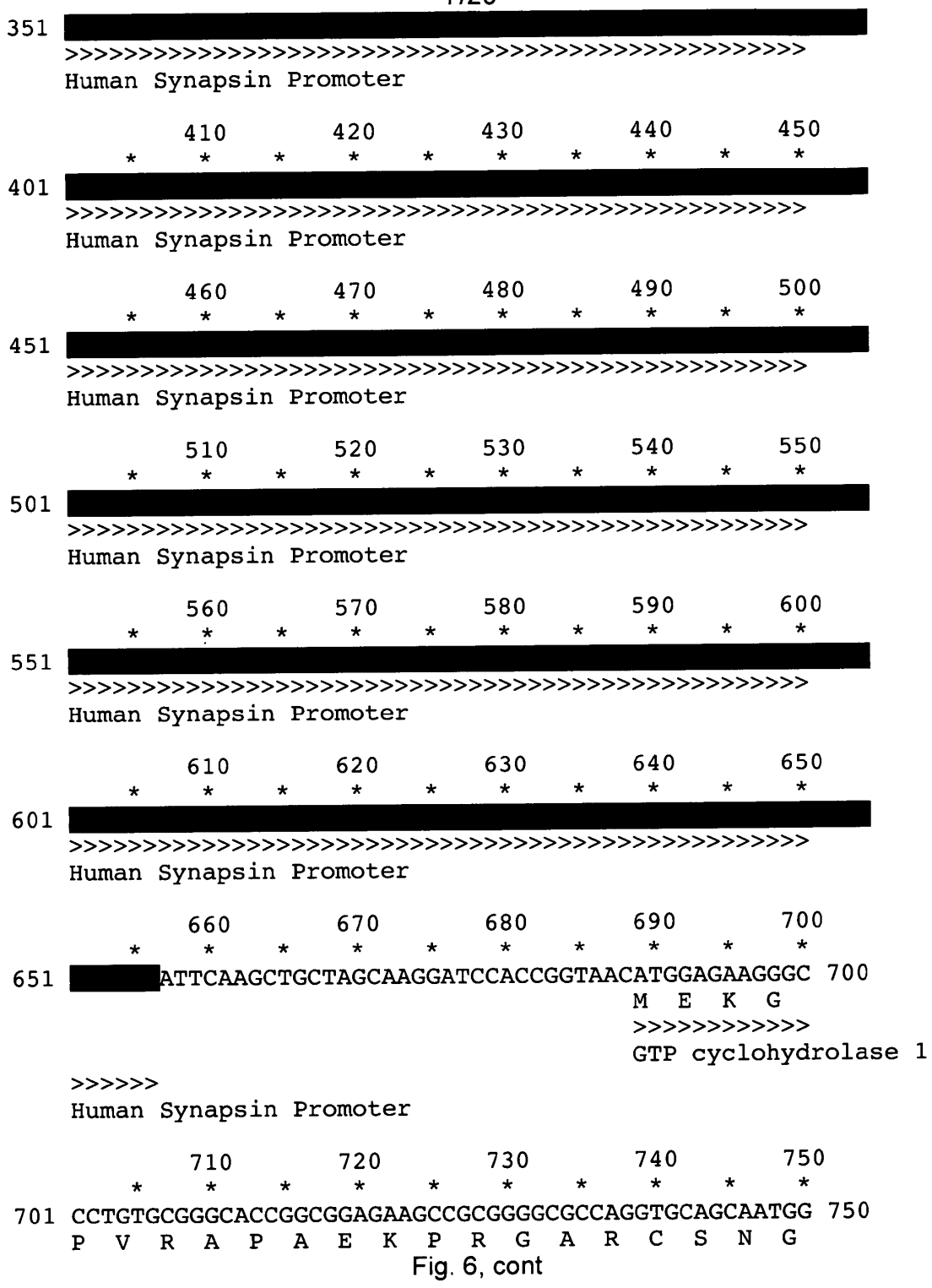

351
>>
Human Synapsin Promoter
410 420 430 440 450
401
>>
Human Synapsin Promoter
460 470 480 490 500
451
>>
Human Synapsin Promoter
510 520 530 540 550
501
>>
Human Synapsin Promoter
560 570 580 590 600
551
>>
Human Synapsin Promoter
610 620 630 640 650
601
>>
Human Synapsin Promoter
660 670 680 690 700
651 ATTCAAGCTGCTAGCAAGGATCCACCGGTAACATGGAGAAGGGC 700
M E K G
>>>>>>>>>>>>
GTP cyclohydrolase 1
>>>>>>
Human Synapsin Promoter
710 720 730 740 750
701 CCTGTGCGGGCACCGGCGGAGAAGCCGCGGGGCGCCAGGTGCAGCAATGG 750
P V R A P A E K P R G A R C S N G

Fig. 6, cont

```
>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
GTP cyclohydrolase 1 isoform 1

         760       770       780       790       800
     *    *    *    *    *    *    *    *    *    *
751 GTTCCCCGAGCGGGATCCGCCGCGGCCCGGGCCCAGCAGGCCGGCGGAGA 800
     F  P  E  R  D  P  P  R  P  G  P  S  R  P  A  E  K
>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
GTP cyclohydrolase 1 isoform 1

         810       820       830       840       850
     *    *    *    *    *    *    *    *    *    *
801 AGCCCCCGCGGCCCGAGGCCAAGAGCGCGCAGCCCGCGGACGGCTGGAAG 850
       P  P  R  P  E  A  K  S  A  Q  P  A  D  G  W  K
>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
GTP cyclohydrolase 1 isoform 1

         860       870       880       890       900
     *    *    *    *    *    *    *    *    *    *
851 GGCGAGCGGCCCCGCAGCGAGGAGGATAACGAGCTGAACCTCCCTAACCT 900
     G  E  R  P  R  S  E  E  D  N  E  L  N  L  P  N  L
>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
GTP cyclohydrolase 1 isoform 1

         910       920       930       940       950
     *    *    *    *    *    *    *    *    *    *
901 GGCAGCCGCCTACTCGTCCATCCTGAGCTCGCTGGGCGAGAACCCCCAGC 950
     A  A  A  Y  S  S  I  L  S  S  L  G  E  N  P  Q  R
>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
GTP cyclohydrolase 1 isoform 1

         960       970       980       990      1000
     *    *    *    *    *    *    *    *    *    *
951 GGCAAGGGCTGCTCAAGACGCCCTGGAGGGCGGCCTCGGCCATGCAGTTC 1000
       Q  G  L  L  K  T  P  W  R  A  A  S  A  M  Q  F
>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
GTP cyclohydrolase 1 isoform 1

        1010      1020      1030      1040      1050
     *    *    *    *    *    *    *    *    *    *
1001 TTCACCAAGGGCTACCAGGAGACCATCTCAGATGTCCTAAACGATGCTAT 1050
     F  T  K  G  Y  Q  E  T  I  S  D  V  L  N  D  A  I
>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
GTP cyclohydrolase 1 isoform 1

        1060      1070      1080      1090      1100
     *    *    *    *    *    *    *    *    *    *
```

Fig. 6, cont

```
1051 ATTTGATGAAGATCATGATGAGATGGTGATTGTGAAGGACATAGACATGT 1100
      F  D  E  D  H  D  E  M  V  I  V  K  D  I  D  M  F
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     GTP cyclohydrolase 1 isoform 1

            1110       1120       1130       1140       1150
         *     *     *     *     *     *     *     *     *     *
1101 TTTCCATGTGTGAGCATCACTTGGTTCCATTTGTTGGAAAGGTCCATATT 1150
       S  M  C  E  H  H  L  V  P  F  V  G  K  V  H  I
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     GTP cyclohydrolase 1 isoform 1

            1160       1170       1180       1190       1200
         *     *     *     *     *     *     *     *     *     *
1151 GGTTATCTTCCTAACAAGCAAGTCCTTGGCCTCAGCAAACTTGCGAGGAT 1200
     G  Y  L  P  N  K  Q  V  L  G  L  S  K  L  A  R  I
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     GTP cyclohydrolase 1 isoform 1

            1210       1220       1230       1240       1250
         *     *     *     *     *     *     *     *     *     *
1201 TGTAGAAATCTATAGTAGAAGACTACAAGTTCAGGAGCGCCTTACAAAAC 1250
      V  E  I  Y  S  R  R  L  Q  V  Q  E  R  L  T  K  Q
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     GTP cyclohydrolase 1 isoform 1

            1260       1270       1280       1290       1300
         *     *     *     *     *     *     *     *     *     *
1251 AAATTGCTGTAGCAATCACGGAAGCCTTGCGGCCTGCTGGAGTCGGGGTA 1300
       I  A  V  A  I  T  E  A  L  R  P  A  G  V  G  V
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     GTP cyclohydrolase 1 isoform 1

            1310       1320       1330       1340       1350
         *     *     *     *     *     *     *     *     *     *
1301 GTGGTTGAAGCAACACACATGTGTATGGTAATGCGAGGTGTACAGAAAAT 1350
     V  V  E  A  T  H  M  C  M  V  M  R  G  V  Q  K  M
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     GTP cyclohydrolase 1 isoform 1

            1360       1370       1380       1390       1400
         *     *     *     *     *     *     *     *     *     *
1351 GAACAGCAAAACTGTGACCAGCACAATGTTGGGTGTGTTCCGGGAGGATC 1400
      N  S  K  T  V  T  S  T  M  L  G  V  F  R  E  D  P
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     GTP cyclohydrolase 1 isoform 1
```

Fig. 6, cont

```
          1410       1420       1430       1440       1450
      *    *    *    *    *    *    *    *    *    *
1401 CAAAGACTCGGGAAGAGTTCCTGACTCTCATTAGGAGCTAATGCATCCCC 1450
       K  T  R  E  E  F  L  T  L  I  R
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     GTP cyclohydrolase 1 isoform 1

          1460       1470       1480       1490       1500
      *    *    *    *    *    *    *    *    *    *
1451 ATCGATGATCCAGACATGATAAGATACATTGATGAGTTTGGACAAACCAC 1500
           >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
           SV40 late polyA

          1510       1520       1530       1540       1550
      *    *    *    *    *    *    *    *    *    *
1501 AACTAGAATGCAGTGAAAAAAATGCTTTATTTGTGAAATTTGTGATGCTA 1550
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     SV40 late polyA

          1560       1570       1580       1590       1600
      *    *    *    *    *    *    *    *    *    *
1551 TTGCTTTATTTGTAACCATTATAAGCTGCAATAAACAAGTTAACAACAAC 1600
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     SV40 late polyA

          1610       1620       1630       1640       1650
      *    *    *    *    *    *    *    *    *    *
1601 AATTGCATTCATTTTATGTTTCAGGTTCAGGGGGAGGTGTGGGAGGTTTT 1650
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     SV40 late polyA

          1660       1670       1680       1690       1700
      *    *    *    *    *    *    *    *    *    *
1651 TTAGTCGACCGAATTGGCCGCT[redacted]
                          >>>>>>>>>>>>>>>>>>>>>>>>>>>
                          Human Synapsin Promoter
     >>
     SV40 late polyA

          1710       1720       1730       1740       1750
      *    *    *    *    *    *    *    *    *    *
1701 [redacted]
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     Human Synapsin Promoter

          1760       1770       1780       1790       1800
      *    *    *    *    *    *    *    *    *    *
```

Fig. 1, cont

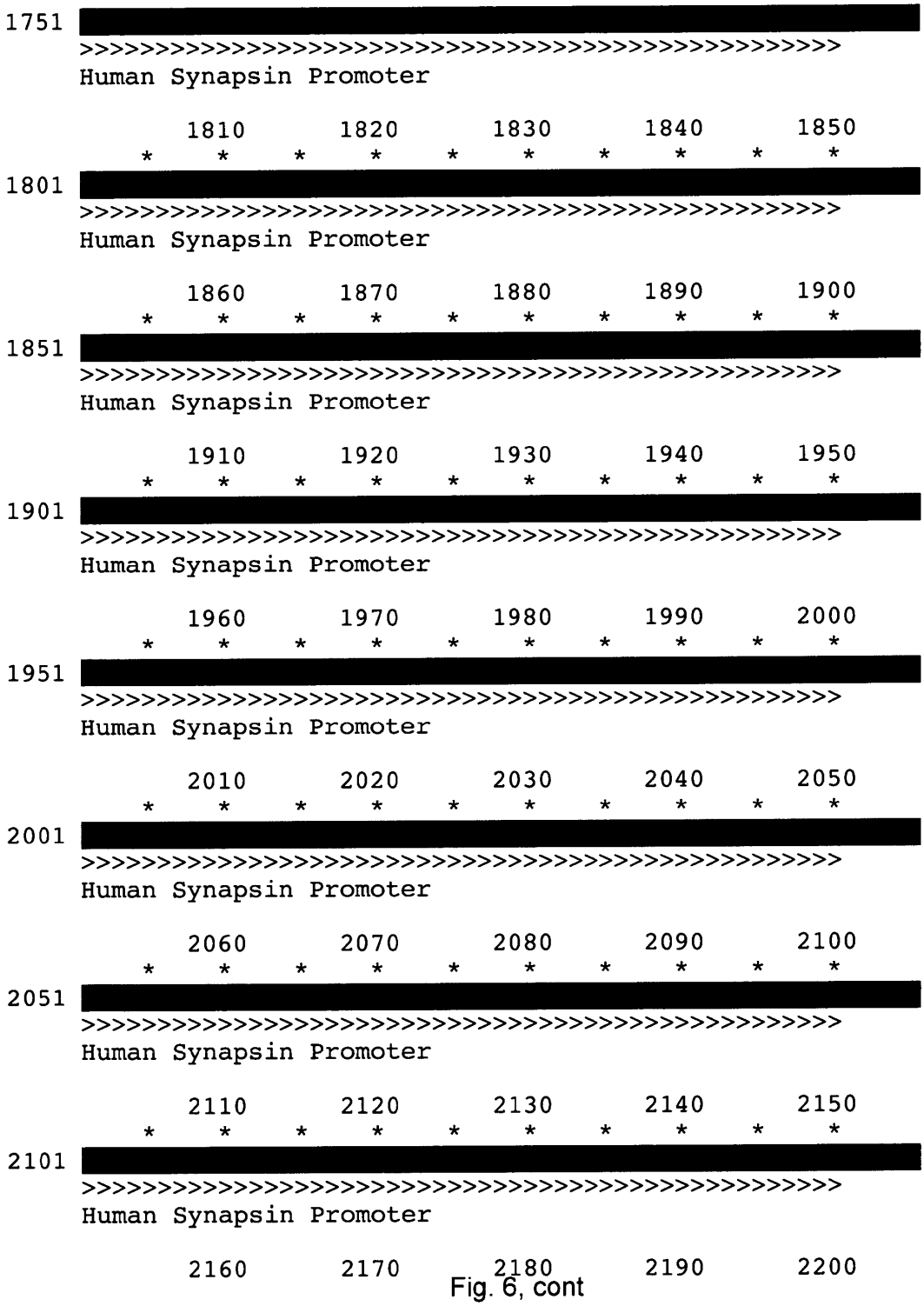

1751
>>
Human Synapsin Promoter
1810 1820 1830 1840 1850
1801
>>
Human Synapsin Promoter
1860 1870 1880 1890 1900
1851
>>
Human Synapsin Promoter
1910 1920 1930 1940 1950
1901
>>
Human Synapsin Promoter
1960 1970 1980 1990 2000
1951
>>
Human Synapsin Promoter
2010 2020 2030 2040 2050
2001
>>
Human Synapsin Promoter
2060 2070 2080 2090 2100
2051
>>
Human Synapsin Promoter
2110 2120 2130 2140 2150
2101
>>
Human Synapsin Promoter
2160 2170 2180 2190 2200

Fig. 6, cont

```
     *    *    *    *    *    *    *    *    *    *
2151 [redacted]ATTCAAGCTGCTAGCAAGGATCCACCGGTCACCATGCCCACCCC 2200
                                          M  P  T  P
     >>>>>>                               >>>>>>>>>>>
     Human Synapsin Promoter              tyrosine hydroxylase

          2210      2220      2230      2240      2250
     *    *    *    *    *    *    *    *    *    *
2201 CGACGCCACCACGCCACAGGCCAAGGGCTTCCGCAGGGCCGTGTCTGAGC 2250
      D  A  T  T  P  Q  A  K  G  F  R  R  A  V  S  E  L
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

          2260      2270      2280      2290      2300
     *    *    *    *    *    *    *    *    *    *
2251 TGGACGCCAAGCAGGCAGAGGCCATCATGTCCCCGCGGTTCATTGGGCGC 2300
       D  A  K  Q  A  E  A  I  M  S  P  R  F  I  G  R
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

          2310      2320      2330      2340      2350
     *    *    *    *    *    *    *    *    *    *
2301 AGGCAGAGCCTCATCGAGGACGCCCGCAAGGAGCGGGAGGCGGCGGTGGC 2350
     R  Q  S  L  I  E  D  A  R  K  E  R  E  A  A  V  A
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

          2360      2370      2380      2390      2400
     *    *    *    *    *    *    *    *    *    *
2351 AGCAGCGGCCGCTGCAGTCCCCTCGGAGCCCGGGGACCCCCTGGAGGCTG 2400
      A  A  A  A  A  V  P  S  E  P  G  D  P  L  E  A  V
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

          2410      2420      2430      2440      2450
     *    *    *    *    *    *    *    *    *    *
2401 TGGCCTTTGAGGAGAAGGAGGGGAAGGCCGTGCTAAACCTGCTCTTCTCC 2450
       A  F  E  E  K  E  G  K  A  V  L  N  L  L  F  S
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

          2460      2470      2480      2490      2500
     *    *    *    *    *    *    *    *    *    *
2451 CCGAGGGCCACCAAGCCCTCGGCGCTGTCCCGAGCTGTGAAGGTGTTTGA 2500
     P  R  A  T  K  P  S  A  L  S  R  A  V  K  V  F  E
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a
```

Fig. 6, cont

```
          2510      2520      2530      2540      2550
       *    *    *    *    *    *    *    *    *    *
2501 GACGTTTGAAGCCAAAATCCACCATCTAGAGACCCGGCCCGCCCAGAGGC 2550
      T  F  E  A  K  I  H  H  L  E  T  R  P  A  Q  R  P
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

          2560      2570      2580      2590      2600
       *    *    *    *    *    *    *    *    *    *
2551 CGCGAGCTGGGGGCCCCCACCTGGAGTACTTCGTGCGCCTCGAGGTGCGC 2600
       R  A  G  G  P  H  L  E  Y  F  V  R  L  E  V  R
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

          2610      2620      2630      2640      2650
       *    *    *    *    *    *    *    *    *    *
2601 CGAGGGGACCTGGCCGCCCTGCTCAGTGGTGTGCGCCAGGTGTCAGAGGA 2650
     R  G  D  L  A  A  L  L  S  G  V  R  Q  V  S  E  D
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

          2660      2670      2680      2690      2700
       *    *    *    *    *    *    *    *    *    *
2651 CGTGCGCAGCCCCGCGGGGCCCAAGGTCCCCTGGTTCCCAAGAAAAGTGT 2700
      V  R  S  P  A  G  P  K  V  P  W  F  P  R  K  V  S
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

          2710      2720      2730      2740      2750
       *    *    *    *    *    *    *    *    *    *
2701 CAGAGCTGGACAAGTGTCATCACCTGGTCACCAAGTTCGACCCTGACCTG 2750
       E  L  D  K  C  H  H  L  V  T  K  F  D  P  D  L
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

          2760      2770      2780      2790      2800
       *    *    *    *    *    *    *    *    *    *
2751 GACTTGGACCACCCGGGCTTCTCGGACCAGGTGTACCGCCAGCGCAGGAA 2800
     D  L  D  H  P  G  F  S  D  Q  V  Y  R  Q  R  R  K
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

          2810      2820      2830      2840      2850
       *    *    *    *    *    *    *    *    *    *
2801 GCTGATTGCTGAGATCGCCTTCCAGTACAGGCACGGCGACCCGATTCCCC 2850
      L  I  A  E  I  A  F  Q  Y  R  H  G  D  P  I  P  R
```

Fig. 6, cont

```
>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
tyrosine hydroxylase isoform a

       2860      2870      2880      2890      2900
    *    *    *    *    *    *    *    *    *    *
2851 GTGTGGAGTACACCGCCGAGGAGATTGCCACCTGGAAGGAGGTCTACACC 2900
  V  E  Y  T  A  E  E  I  A  T  W  K  E  V  Y  T
>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
tyrosine hydroxylase isoform a

       2910      2920      2930      2940      2950
    *    *    *    *    *    *    *    *    *    *
2901 ACGCTGAAGGGCCTCTACGCCACGCACGCCTGCGGGGAGCACCTGGAGGC 2950
T  L  K  G  L  Y  A  T  H  A  C  G  E  H  L  E  A
>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
tyrosine hydroxylase isoform a

       2960      2970      2980      2990      3000
    *    *    *    *    *    *    *    *    *    *
2951 CTTTGCTTTGCTGGAGCGCTTCAGCGGCTACCGGGAAGACAATATCCCCC 3000
 F  A  L  L  E  R  F  S  G  Y  R  E  D  N  I  P  Q
>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
tyrosine hydroxylase isoform a

       3010      3020      3030      3040      3050
    *    *    *    *    *    *    *    *    *    *
3001 AGCTGGAGGACGTCTCCCGCTTCCTGAAGGAGCGCACGGGCTTCCAGCTG 3050
  L  E  D  V  S  R  F  L  K  E  R  T  G  F  Q  L
>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
tyrosine hydroxylase isoform a

       3060      3070      3080      3090      3100
    *    *    *    *    *    *    *    *    *    *
3051 CGGCCTGTGGCCGGCCTGCTGTCCGCCCGGGACTTCCTGGCCAGCCTGGC 3100
R  P  V  A  G  L  L  S  A  R  D  F  L  A  S  L  A
>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
tyrosine hydroxylase isoform a

       3110      3120      3130      3140      3150
    *    *    *    *    *    *    *    *    *    *
3101 CTTCCGCGTGTTCCAGTGCACCCAGTATATCCGCCACGCGTCCTCGCCCA 3150
 F  R  V  F  Q  C  T  Q  Y  I  R  H  A  S  S  P  M
>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
tyrosine hydroxylase isoform a

       3160      3170      3180      3190      3200
    *    *    *    *    *    *    *    *    *    *
```

Fig. 6, cont

```
3151 TGCACTCCCCTGAGCCGGACTGCTGCCACGAGCTGCTGGGGCACGTGCCC 3200
       H  S  P  E  P  D  C  C  H  E  L  L  G  H  V  P
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

            3210       3220       3230       3240       3250
         *     *     *     *     *     *     *     *     *     *
3201 ATGCTGGCCGACCGCACCTTCGCGCAGTTCTCGCAGGACATTGGCCTGGC 3250
     M  L  A  D  R  T  F  A  Q  F  S  Q  D  I  G  L  A
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

            3260       3270       3280       3290       3300
         *     *     *     *     *     *     *     *     *     *
3251 GTCCCTGGGGGCCTCGGATGAGGAAATTGAGAAGCTGTCCACGCTGTACT 3300
      S  L  G  A  S  D  E  E  I  E  K  L  S  T  L  Y  W
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

            3310       3320       3330       3340       3350
         *     *     *     *     *     *     *     *     *     *
3301 GGTTCACGGTGGAGTTCGGGCTGTGTAAGCAGAACGGGGAGGTGAAGGCC 3350
       F  T  V  E  F  G  L  C  K  Q  N  G  E  V  K  A
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

            3360       3370       3380       3390       3400
         *     *     *     *     *     *     *     *     *     *
3351 TATGGTGCCGGGCTGCTGTCCTCCTACGGGGAGCTCCTGCACTGCCTGTC 3400
     Y  G  A  G  L  L  S  S  Y  G  E  L  L  H  C  L  S
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

            3410       3420       3430       3440       3450
         *     *     *     *     *     *     *     *     *     *
3401 TGAGGAGCCTGAGATTCGGGCCTTCGACCCTGAGGCTGCGGCCGTGCAGC 3450
      E  E  P  E  I  R  A  F  D  P  E  A  A  A  V  Q  P
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

            3460       3470       3480       3490       3500
         *     *     *     *     *     *     *     *     *     *
3451 CCTACCAAGACCAGACGTACCAGTCAGTCTACTTCGTGTCTGAGAGCTTC 3500
       Y  Q  D  Q  T  Y  Q  S  V  Y  F  V  S  E  S  F
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a
```

Fig. 6, cont

```
          3510       3520       3530       3540       3550
     *    *    *    *    *    *    *    *    *    *
3501 AGTGACGCCAAGGACAAGCTCAGGAGCTATGCCTCACGCATCCAGCGCCC 3550
     S  D  A  K  D  K  L  R  S  Y  A  S  R  I  Q  R  P
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

          3560       3570       3580       3590       3600
     *    *    *    *    *    *    *    *    *    *
3551 CTTCTCCGTGAAGTTCGACCCGTACACGCTGGCCATCGACGTGCTGGACA 3600
      F  S  V  K  F  D  P  Y  T  L  A  I  D  V  L  D  S
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

          3610       3620       3630       3640       3650
     *    *    *    *    *    *    *    *    *    *
3601 GCCCCCAGGCCGTGCGGCGCTCCCTGGAGGGTGTCCAGGATGAGCTGGAC 3650
       P  Q  A  V  R  R  S  L  E  G  V  Q  D  E  L  D
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

          3660       3670       3680       3690       3700
     *    *    *    *    *    *    *    *    *    *
3651 ACCCTTGCCCATGCGCTGAGTGCCATTGGCTAACTAGTGGATCCGTCGAC 3700
     T  L  A  H  A  L  S  A  I
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     tyrosine hydroxylase isoform a

          3710       3720       3730       3740       3750
     *    *    *    *    *    *    *    *    *    *
3701 AATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAA 3750
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     WPRE

          3760       3770       3780       3790       3800
     *    *    *    *    *    *    *    *    *    *
3751 CTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGT 3800
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     WPRE

          3810       3820       3830       3840       3850
     *    *    *    *    *    *    *    *    *    *
3801 ATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTATAAA 3850
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     WPRE
```

Fig. 6, cont

```
          3860       3870       3880       3890       3900
      *    *    *    *    *    *    *    *    *    *
3851 TCCTGGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAACG 3900
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     WPRE

          3910       3920       3930       3940       3950
      *    *    *    *    *    *    *    *    *    *
3901 TGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTGGGGCA 3950
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     WPRE

          3960       3970       3980       3990       4000
      *    *    *    *    *    *    *    *    *    *
3951 TTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCCT 4000
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     WPRE

          4010       4020       4030       4040       4050
      *    *    *    *    *    *    *    *    *    *
4001 ATTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGG 4050
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     WPRE

          4060       4070       4080       4090       4100
      *    *    *    *    *    *    *    *    *    *
4051 GGCTCGGCTGTTGGGCACTGACAATTCCGTGGTGTTGTCGGGGAAGCTGA 4100
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     WPRE

          4110       4120       4130       4140       4150
      *    *    *    *    *    *    *    *    *    *
4101 CGTCCTTTCCATGGCTGCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGG 4150
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     WPRE

          4160       4170       4180       4190       4200
      *    *    *    *    *    *    *    *    *    *
4151 ACGTCCTTCTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTC 4200
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     WPRE

          4210       4220       4230       4240       4250
      *    *    *    *    *    *    *    *    *    *
4201 CCGCGGCCTGCTGCCGGCTCTGCGGCCTCTTCCGCGTCTTCGCCTTCGCC 4250
     >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
     WPRE
```

Fig. 6, cont

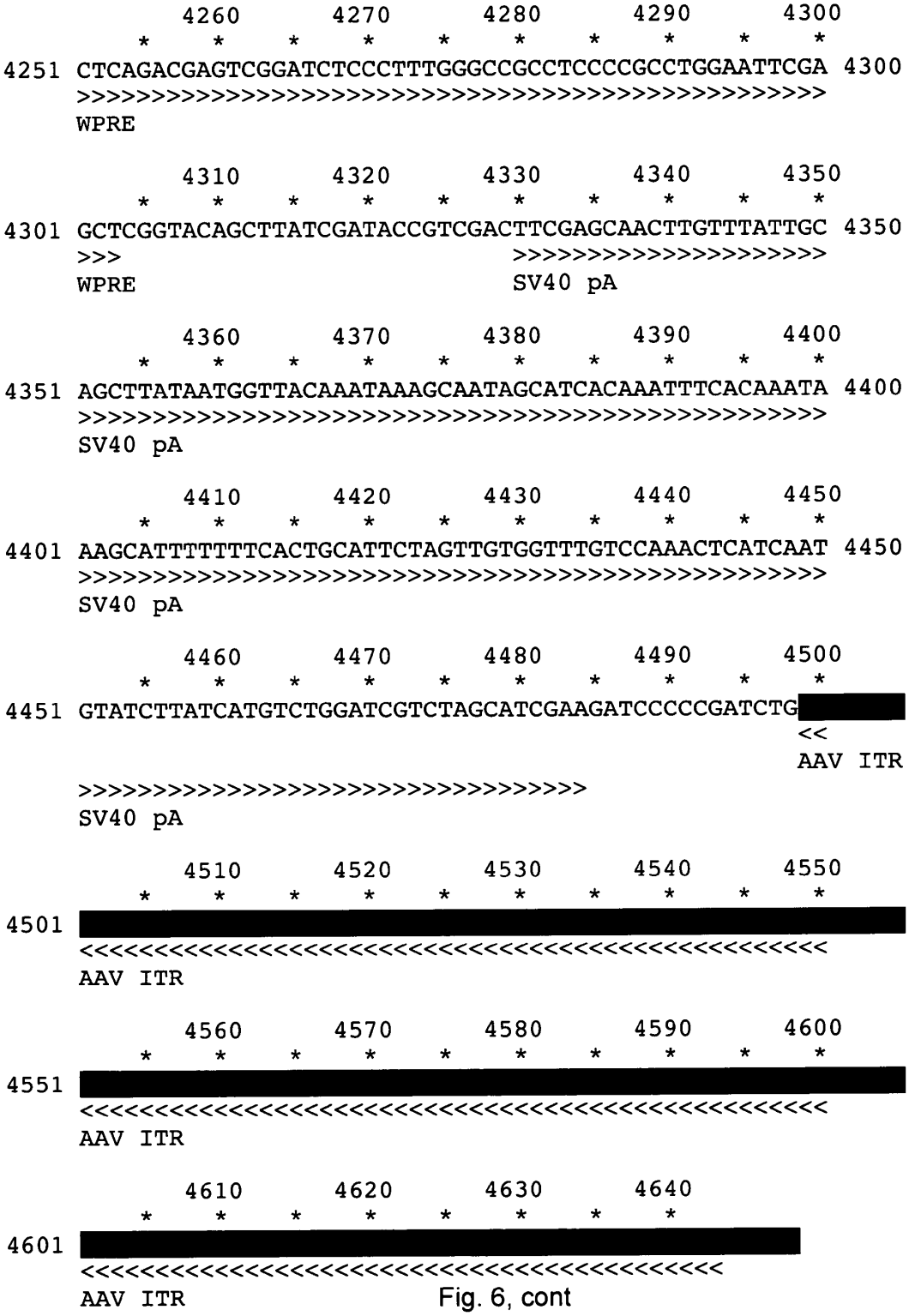

4260 4270 4280 4290 4300
4251 CTCAGACGAGTCGGATCTCCCTTTGGGCCGCCTCCCCGCCTGGAATTCGA 4300
>>>
WPRE
4310 4320 4330 4340 4350
4301 GCTCGGTACAGCTTATCGATACCGTCGACTTCGAGCAACTTGTTTATTGC 4350
>>> >>>>>>>>>>>>>>>>>>>
WPRE SV40 pA
4360 4370 4380 4390 4400
4351 AGCTTATAATGGTTACAAATAAAGCAATAGCATCACAAATTTCACAAATA 4400
>>>
SV40 pA
4410 4420 4430 4440 4450
4401 AAGCATTTTTTTCACTGCATTCTAGTTGTGGTTTGTCCAAACTCATCAAT 4450
>>>
SV40 pA
4460 4470 4480 4490 4500
4451 GTATCTTATCATGTCTGGATCGTCTAGCATCGAAGATCCCCCGATCTG
<<
AAV ITR
>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
SV40 pA
4510 4520 4530 4540 4550
4501
<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<
AAV ITR
4560 4570 4580 4590 4600
4551
<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<
AAV ITR
4610 4620 4630 4640
4601
<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<
AAV ITR

Fig. 6, cont

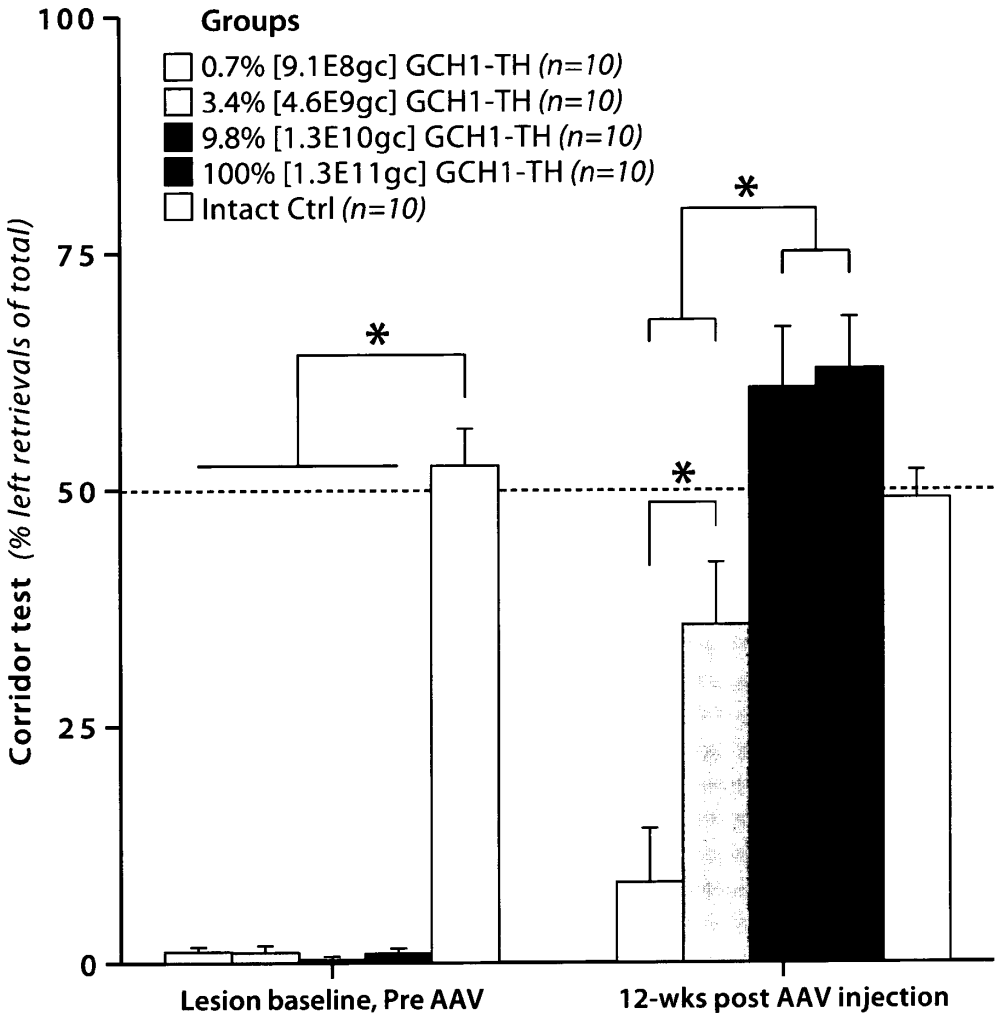

Groups
0.7% [9.1E8gc] GCH1-TH (n=10)
3.4% [4.6E9gc] GCH1-TH (n=10)
9.8% [1.3E10gc] GCH1-TH (n=10)
100% [1.3E11gc] GCH1-TH (n=10)
Intact Ctrl (n=10)
Corridor test (% left retrievals of total)
100
75
50
25
0
*
*
*
Lesion baseline, Pre AAV
12-wks post AAV injection

Fig. 7

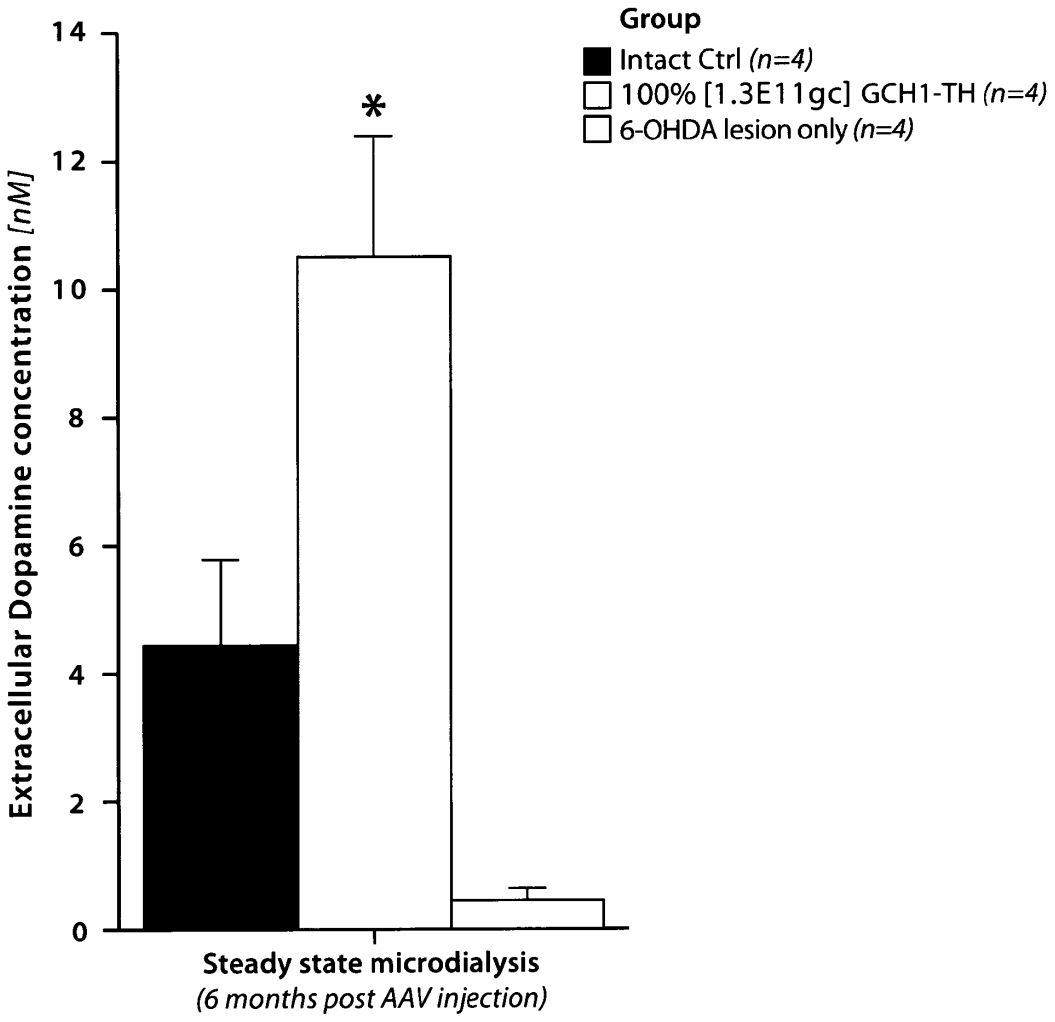

Group
Intact Ctrl (n=4)
100% [1.3E11gc] GCH1-TH (n=4)
6-OHDA lesion only (n=4)
Extracellular Dopamine concentration [nM]
14
12
10
8
6
4
2
0
*
Steady state microdialysis
(6 months post AAV injection)

Fig. 8